REMARKS

Claims 1, 3-5, 9-25 and 32 are pending in the present application. Claims 2, 6-8, 16-19, 22, 26-31 and 33-45 have been canceled without prejudice or disclaimer. Claims 1, 3-5, 12, 14, 20-21, 23-25 and 32 have been amended.

Applicants, by canceling or amending any claims, make no admission as to the validity of any rejection made by the Examiner against any such claims. Applicants reserve the right to reassert any of the claims canceled and/or the original claim scope of any claim amended, in a continuing application.

Claim 1 has been amended to recite a "method for treating an inflammatory disease, disorder or cancer in a patient, comprising: simultaneous or step-wise administering of curcumin and at least one NSAID to the patient, the curcumin being in an amount sufficient to reduce the NSAID concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID alone, wherein the NSAID is selected from the group consisting of ketorolac, nabumetone, salsalate, diclofenac, indomethacin, nabumetone, phenylbutazone, oxyphenbutazone, dipyrone, ramifenazone, tenoxicam, valdecoxib, parecoxib, etoricoxib, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, naproxen sodium, rofecoxib, nimesulide, aspirin, tolmetin, fenoprofen, flurbiprofen, loxoprofen, vedaprofen, meclofenamic acid, meclofenamate sodium, tolfenamic acid, acetaminophen, flunixin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac and diflunisal, or a salt or prodrug thereof." Support for this amendment can be found throughout the specification and claims as originally filed.

Claims 12 and 32 have also been amended to incorporate the Markush group of NSAIDS incorporated into claim 1. Claims 3-5, 12, 14, 20-21, 23-25 and 32 have been amended to correct dependency and other formality issues in view of US patent practice and the amendments to claims 1, 12 and 32. Support for the amendments to claims 3-5, 12, 14, 20-21, 23-25 and 32 can be found throughout the specification and claims as originally filed

No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claims 35-41 have been rejected under 35 USC § 101.

The Examiner asserts that claims 35-41 are directed to non-statutory subject matter because the claims encompass both a "process" of use and a process of making.

Applicants note that claims 35-41 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 35-41, this rejection has been rendered moot. Accordingly, reconsideration and withdrawal of this rejection is respectfully rejected.

II. At pages 3 and 4 of the Official Action, claims 2-4, 10, 11, 25, 34-41 and 43 have been rejected under 35 USC § 112, second paragraph.

The Examiner asserts that claims 2-4, 10, 11, 25, 34-41 and 43 are indefinite for the reasons set forth in the Official Action.

Applicants respectfully submit that claims 2, 34-41 and 43 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 2, 34-41 and 43, the

rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 2, 34-41 and 43 is respectfully rejected.

In addition, Applicants submit that the amendments to the presently pending claims submitted herein obviate each of the Examiner's remaining rejections to the present claims under 35 USC § 112, second paragraph. For example, Applicants note that the claims are no longer directed derivatives or analogues of various NSAIDS. Further, Applicants note that claim 25 no longer recites "and other agents suitable for combination therapy." Accordingly, reconsideration and withdrawal of the rejection of claims 3-4, 10, 11 and 25 is respectfully rejected.

In view of the foregoing, Applicants respectfully submit that all of the pending claims are clear and definite within the meaning of 35 USC § 112. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

III. At pages 5-8 of the Official Action, claims 7, 16, 19-21, 25-28, 30, 32 and 34 have been rejected under 35 USC § 112, first paragraph.

The Examiner asserts that, while the specification is enabling for inhibiting cancer cell growth in a subject, the specification is not enabling for preventing or treating cancer or reducing the likelihood of contracting cancer in a subject susceptible to contracting said disease.

Applicants respectfully submit that claims 7, 16, 19, 26-28, 30 and 34 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 7, 16, 19, 26-28, 30 and 34, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 7, 16, 19, 26-28, 30 and 34 is

respectfully rejected.

In addition, Applicants note that claims 20-21 and 25 now each depend, either directly or indirectly, from claim 1. In addition, claim 32 is an independent claim directed to a composition. Applicants submit that since claims 20-21 and 25 are dependent from a non-rejected base claim, and claim 32 is not directed to a method at all, the rejection of claims 20-21, 25 and 32 has been obviated. Accordingly, reconsideration and withdrawal of the rejection of claims 20-21, 25 and 32 is respectfully rejected.

In view of the foregoing, Applicant submits that the instant application enables the skilled artisan to make and use the full scope of the invention as claimed, within the meaning of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 9 of the Official Action, claims 1, 5-24 and 26-41 have been rejected under 35 USC § 102(b) as being anticipated by Metaproteomics LLC (International Application Publication No. WO 03/007975).

The Examiner asserts that Metaproteomics LLC describe every element of claims 1, 5-24 and 26-41.

Applicants respectfully submit that claims 6-8, 16-19, 22 and 33-41 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 6-8, 16-19, 22 and 33-41, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 6-8, 16-19, 22 and 33-41 is respectfully rejected.

In view of the following, the rejection of claims 1, 5, 9-15, 20-21, 23-24 and 26-32 is respectfully traversed.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. R*ichardson v. Suzuki Motor Co.,* 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond,* 15 USPQ2d 1566 (Fed. Cir. 1990).

Independent claim 1 is directed to a method for treating an inflammatory disease, disorder or cancer in a patient, comprising: simultaneous or step-wise administering of curcumin and at least one NSAID to the patient, the curcumin being in an amount sufficient to reduce the NSAID concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID alone, wherein the NSAID is selected from the group consisting of ketorolac, nabumetone, salsalate, diclofenac, indomethacin, nabumetone, phenylbutazone, oxyphenbutazone, dipyrone, ramifenazone, tenoxicam, valdecoxib, parecoxib, etoricoxib, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, naproxen sodium, rofecoxib, nimesulide, aspirin, tolmetin, fenoprofen, flurbiprofen, loxoprofen, vedaprofen, meclofenamic acid, meclofenamate sodium, tolfenamic acid, acetaminophen, flunixin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac and diflunisal, or a salt or prodrug thereof. Claims 5, 9, 10, 20-21, 23-24 and 26-31 depend, either directly or indirectly, from claim 1.

Independent claim 12 is directed to a method for inhibiting cancer cell growth, comprising: contacting cancer cells with an effective amount of a formulation comprising

curcumin and at least one NSAID selected from the group consisting of ketorolac, nabumetone, salsalate, diclofenac, indomethacin, nabumetone, phenylbutazone, oxyphenbutazone, dipyrone, ramifenazone, tenoxicam, valdecoxib, parecoxib, etoricoxib, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, naproxen sodium, rofecoxib, nimesulide, aspirin, tolmetin, fenoprofen, flurbiprofen, loxoprofen, vedaprofen, meclofenamic acid, meclofenamate sodium, tolfenamic acid, acetaminophen, flunixin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac and diflunisal, or a salt or prodrug thereof. Claims 13-15 depend, either directly or indirectly, from claim 12.

Independent claim 32 is directed to combination of two pharmaceutical compositions, comprising: a first composition comprising an effective amount of at least one NSAID drug selected from the group consisting of ketorolac, nabumetone, salsalate, diclofenac, indomethacin, nabumetone, phenylbutazone, oxyphenbutazone, dipyrone, ramifenazone, tenoxicam, valdecoxib, parecoxib, etoricoxib, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, naproxen sodium, rofecoxib, nimesulide, aspirin, tolmetin, fenoprofen, flurbiprofen, loxoprofen, vedaprofen, meclofenamic acid, meclofenamate sodium, tolfenamic acid, acetaminophen, flunixin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac and diflunisal, or a salt or prodrug thereof; and a second composition comprising an effective amount of curcumin, the combination is intended for administering to a subject for treatment of cancer or inflammation, wherein said second composition is administered after administering said first composition.

In contrast, Metaproteomics LLC is directed to synergistic compositions comprising curcuminoids and NSAIDs such as ditropen lactone species and trierpene species. In addition as described at page 5, lines 7-10 of Metaproteomics LLC, "provides a combination comprising, as a first compound, a curcuminoid species, and as a second compound, a compound that would specifically and synergistically enhance the anti-inflammatory effect of the curcuminoid." Therefore, Applicants submit that Metaproteomics LLC demonstrates a combination of the two components which employ concentrations acceptable in mono-therapy.

However, Applicants submit that Metaproteomics LLC do not teach NSAIDs recited in the presently pending claims. In addition, Applicants submit that Metaproteomics LLC do not teach the curcumin being in an amount sufficient to reduce the NSAID concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID alone," as presently recited, for example, in claim 1. Therefore, since Metaproteomics LLC do not teach every element of the presently pending claims, Applicants submit that claims 1, 5, 9-15, 20-21, 23-24 and 26-32 are not anticipated by Metaproteomics LLC.

In view of the foregoing, Applicants respectfully submit that the presently pending claims are novel. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

V. At page 10 of the Official Action, claims 18-25, 33 and 34 have been rejected under 35 USC § 102(b) as being anticipated by Gelber et al. (US Patent Application Publication No. 2001/004410).

The Examiner asserts that Gelber et al. describe every element of claims 18-25, 33 and 34.

Applicants respectfully submit that claims 18-19, 33 and 34 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 18-19, 33 and 34and 33-45, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 18-19, 22, 33 and 34 is respectfully rejected.

With regard to claims 20-21 and 23-25, Applicants submit that each of these claims has been amended to depend, either directly or indirectly from non-rejected claim 1. As such, Applicants submit that the rejection of claims 20-21 and 23-25 has been obviated. Accordingly, reconsideration and withdrawal of this rejection is respectfully submitted.

VI. At page 10 of the Official Action, claim 29 has been rejected under 35 USC § 102(b) as being anticipated by O'Neil (US Patent No. 4,704,405).

The Examiner asserts that O'Neil describe every element of claim 29.

Applicants respectfully submit that claim 29 has been cancelled without prejudice or disclaimer. In view of the cancellation of claim 29, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claim 29 is respectfully requested.

VII. At page 10 of the Official Action, claims 30 and 31 have been rejected under 35 USC § 102(b) as being anticipated by Arbiser (US Patent No. 6,673,843).

The Examiner asserts that Arbiser describe every element of claims 30 and 31.

Applicants respectfully submit that claims 30 and 31 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 30 and 31, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 30 and 31 is respectfully requested.

VII. At page 12 of the Official Action, claims 2-4 have been rejected under 35 USC § 103(a) as being unpatentable over Metaproteomics LLC in view of Reddy et al. (of record).

The Examiner asserts that Metaproteomics LLC and Reddy et al. teach or suggest every element of claim 2-4.

Applicants respectfully submit that claim 4 has been cancelled without prejudice or disclaimer. In view of the cancellation of claim 4, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claim 4 is respectfully rejected.

In view of the following, the rejection of claims 3 and 4 is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the

background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants submit that a prima facie case of obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest every element of claims 3 and 4.

As discussed, claim 1 is directed to a method for treating an inflammatory disease, disorder or cancer in a patient, comprising: simultaneous or step-wise administering of curcumin and at least one NSAID to the patient, the curcumin being in an amount sufficient to reduce the NSAID concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID alone, wherein the NSAID is selected from the group consisting of ketorolac, nabumetone, salsalate, diclofenac, indomethacin, nabumetone, phenylbutazone, oxyphenbutazone, dipyrone, ramifenazone, tenoxicam,

valdecoxib, parecoxib, etoricoxib, celecoxib, sulindac, sulindac sulfide, exisulind, ibuprofen, naproxen, naproxen sodium, rofecoxib, nimesulide, aspirin, tolmetin, fenoprofen, flurbiprofen, loxoprofen, vedaprofen, meclofenamic acid, meclofenamate sodium, tolfenamic acid, acetaminophen, flunixin, piroxicam, oxaprozin, meloxicam, ketoprofen, etodolac and diflunisal, or a salt or prodrug thereof. Claims 3 and 4 depend, either directly or indirectly from claim 1.

Metaproteomics LLC is discussed in detail above. As discussed, Metaproteomics LLC do not teach or suggest However, Applicants submit that Metaproteomics LLC do not teach NSAIDs recited in the presently pending claims. In addition, Applicants submit that Metaproteomics LLC do not teach the curcumin being in an amount sufficient to reduce the NSAID concentration needed while maintaining the same therapeutic effect as compared to administering the NSAID alone," as presently recited, for example, in claim 1. Therefore, since Metaproteomics LLC do not teach or suggest every element of the presently pending claims, Applicants submit that claims 3 and 4 are not rendered obvious by Metaproteomics LLC.

Reddy et al. do not remedy the deficiencies of Metaproteomics LLC. Reddy et al. is directed to a combination of agents with different modes of action is useful in increasing the efficacy and reducing toxicity. The publication continues to explain that both curcumin and NSAIDs are COX-2 inhibitors, therefore acting through the same biological pathway, exhibiting the same mode of action. It is thus inferred from Reddy et al that a combination of curcumin and an NSAID is not expected to increase efficacy and reduce toxicity (as they each has the same mode of action). Reddy et al thus concludes, that "A novel approach

toward the chemoprevention of colon cancer is to co-administer two or more agents with different modes of action whose aggregate action would be significant, while toxicity would be minimal." *See* Reddy et al. at page 161, right-hand column, lines 4-9.

Neither Metaproteomics nor Reddy et al., taken alone or in combination, teach or suggest the possibility of using curcumin and an NSAID, in NSAID amounts lower than those acceptable in mono-therapy (treatment with an NSAID drug alone), for achieving increased efficacy and lowered toxicity. Reddy et al teaches away from such a combination as the reader is directed to the understanding that a higher efficacy and a lowered toxicity are achievable only where the modes of action are different. As both the NSAIDs of Reddy et al and curcumin exhibit the same mode of action (inhibition of COX-2), their combination is not expected to result in a higher efficacy and a lowered toxicity.

Additionally, a person skilled in the art would not have expected a combination of curcumin and an NSAID, the NSAID being in an amount lower than traditionally prescribed, to be effective in view of the teachings of Metaproteomics and/or Reddy et al. This is the case as each of these documents suggests using a combination which includes therapeutic amounts of each of the agents.

In support of this, Applicants direct the Examiner's attention to the present specification, at page 26, which provides:

> Curcumin augments celecoxib's growth-inhibitory effect in human cancer cell lines in vitro. This observed effect is clinically important, as it can be achieved in the serum of patients receiving standard anti-inflammatory doses of celecoxib. ***Our current results demonstrate that in the presence of low concentrations of curcumin (10-15 μM), a physiological concentration of celecoxib (5 μM) is sufficient to inhibit cell growth by inhibiting proliferation and inducing apoptosis, by COX-2 and non-COX-2 pathways. This effect is similar to that achieved with a 10-fold higher***

> ***concentration of celecoxib (50μM) when administered alone.*** The clinical importance of this effect lies in the fact that it can be achieved in the serum of patients treated with a standard anti-inflammatory (200-400 mg) or anti-neoplastic (400-800 mg) doses of celecoxib. This paves the way for a novel strategy to prevent and treat cancers of various types, given that this approach will involve a regimen of a low profile of side effects. A synergistic effect is also observed in HT-29 and IEC18-K-ras cells that express high levels of COX-2. Only the combined modality regiment reduced the level of COX-2 mRNA and almost entirely diminishing PGE.sub.2 production. At the same time a significant additive growth inhibition was observed in cancer cell lines which express low or no COX-2 activity (e.g. Caco-2 and SW-480). (Emphasis Added).

Applicants submit that, as demonstrated further in the drawings and in the specific examples, a similar effect to that obtained using ***50μM*** of the NSAID in the combination with curcumin, was obtained when the NSAID was used alone in either an anti-inflammatory or anti-neoplastic amount; the anti-inflammatory or anti-neoplastic amount being, as indicated, 10-fold greater. The synergistic effect referred to in the above passage is not the same synergy which is discussed in Metaproteomics LLC.

Applicants submit that the synergistic effect in Metaproteomics LLC results simply from the combination of two mono-therapies, namely the use of agent amounts which by alone exert a therapeutic effect. This is not the case with the combination of the present subject matter as it comprises the NSAID in an amount which is lower than the therapeutic effective amount.

Accordingly, Applicant submits that none of the cited references, whether taken alone or in combination, render the presently claimed subject matter obvious, within the meaning of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claims 3 and 4.

IX. At page 12 of the Official Action, claims 42-45 have been rejected under 35 USC § 103(a) as being unpatentable over Metaproteomics LLC.

Applicants respectfully submit that claims 42-45 have been cancelled without prejudice or disclaimer. In view of the cancellation of claims 42-45, the rejection of the same has been rendered moot. Accordingly, reconsideration and withdrawal of the rejection of claims 42-45 is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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